FDA's Future Plans to Enhance Oversight of High Risk Genetic Tests
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Our next presenter is Dr. Steve Gutman.We're going to hold the questions until the roundtable. Our next presenter is Dr. Steve Gutman, who is director of the Office of In Vitro Diagnostics. Maybe not.

DR. FEIGAL: We pulled a switch on you.

DR. McCABE: Okay. Our next presenter is not Dr. Gutman, but it's Dr. David Feigal, who is director of the FDA's Center for Devices and Radiological Health, and the FDA is ex officio to this committee, and who will share with us the FDA's plans for enhancing the oversight of genetic tests. Thank you.

DR. FEIGAL: Thanks very much. I'm the warm-up act for Dr. Gutman. (Laughter.)

DR. FEIGAL: This is a cover that occurred in Time magazine about two summers ago and made the comment that thanks to a patchwork regulatory system, perhaps a quarter of all research gets no oversight whatsoever. I don't think they actually had investigational diagnostic tests on their radar screen. I think they were talking about other kinds of research. One of the challenges this morning for you to consider that you discussed a little bit with the CLIA program presenters is what is required? What is investigational and what's the appropriate level of oversight in the different ways that diagnostic tests are offered?

It's appropriate to begin by saying what's FDA's oversight? FDA regulates manufacturers, not laboratories, not doctors, manufacturers, and we regulate the manufacturers of medical devices. This is the medical device definition, the part of it that's germane to diagnostics, and it's language that's almost 100 years old, so we still are trying to figure out what a contrivance is. But we regulate those if you make them. (Laughter.)

DR. FEIGAL: But we do regulate in vitro diagnostics, components, parts or accessories, and products which are intended for the diagnosis of disease or other conditions, and things that are used diagnostically that are useful for cure mitigation, treatment or prevention of disease in man.

The basic kinds of consumer protections that FDA has been providing for almost 100 years can be sorted out into a couple of different groupings. One of the important ones is our role in risk/benefit management. We need to decide when is first human use safe, and obviously that's an issue if they're going to put something in your body. But sometimes information itself is important enough that it takes careful consideration to actually design how that new information is going to be used.

Consider, for example, if you're a young woman taking a test to see if you have early ovarian cancer. Since there is no recognized test that can do that already, the issue of how you're going to proceed from there if the test is positive is one that has a lot of implications. So there are times when, in fact, FDA requires protocols for the evaluation of new diagnostic devices and all of the protections of IRBs and informed consent and monitoring.

We have responsibilities for safe investigational use during product development. We control the

access to market for some products but not all. We have responsibilities when products are in widespread use to monitor the use, the adverse experiences, and the corrective actions that are taken. We have the authority ourselves to do recalls when the situation is very serious. We and manufacturers issue warnings and alerts and monitor market withdrawals of products.

There's another grouping of consumer protections which is really what makes FDA different in this country than a lot of other countries. Many countries actually regulate their products in a systems approach by assuring that there's an overall system that will assure quality, but they don't look at any evidence about the product per se. What happened in the FDA law, and it began to really have teeth for drugs in 1962 and for devices in 1976, was to actually set a standard for evidence. The standard for evidence for a new drug is adequate and well-controlled trials. A drug must be studied in humans in clinical trials that are adequate and well controlled.

The evidence standard for devices is more flexible. It's the phrase "valid scientific evidence," which includes clinical trials but also includes performance measures, and in fact most devices actually are studied at the bench and do not have clinical trials as evidence.

But there are many settings, including settings for diagnostic devices, where the only way you'll know it works is to test it in a clinical setting and get that clinical correlation.

There's a third part of our responsibilities which we won't talk about very much today. It's actually one of the more colorful parts of our job, which is integrity assurance, enforcement for fraud, for counterfeit products, for research misconduct, but that really isn't what we're talking about today.

It's helpful if we actually look a little bit at the life cycle of a product and look at where the regulation sort of fits in. So if you begin with an IVD concept, a glimmer in a laboratorian's eye, one of the early steps is to develop the reagents and analytes that make that test run, the brains of the test if you will, and that may be paired with non-clinical specimens that allow you to assess the performance of those analytes.

In fact, if you want to be a reagent manufacturer, this is where you go to market, and there's a special grouping of reagents called analyte-specific reagents which include genetic tests where FDA actually published a classification rule some three or four years ago that outlined manufacturers' responsibilities and labs' responsibilities, and at that time down-classified most of these products.

The default in the device regulations we'll talk about in a moment is that a new product is assumed to be a high-risk product until proven otherwise. What was said with the ASR rule is that if these responsibilities were met by the manufacturer and by the laboratory, then in fact most of these ASRs would be Class I-exempt, and Dr. Gutman, when he follows up, will actually talk in a little more detail about the refinements that we need to the initial approach we took with ASRs.

But the manufacturers must register, tell us who they are, what their products are, and they must follow quality systems regulations, sometimes called good manufacturing practices.

They can only be sold to a high-complexity lab. The labs must establish the performance and labeling. The manufacturer is only selling a reagent. Most, as I mentioned, are exempt from premarket review. The manufacturer, if they are aware of adverse experiences, must file medical device reports to FDA. It's part of a quality system to have such a program.

The laboratory has to be a high-complexity lab. There's no such thing as an off-label use of an ASR where the manufacturer can only sell it but if somebody else uses it, too bad. No, the laboratories must be high complexity. The laboratory is responsible for establishing the performance of the test and the label, and Dr. Gutman will go over what we expect in a manufacturer's label, and there are some things that we've said are mandatory in the labeling, some disclaimers about the test not having been FDA reviewed as a test, and then there are some things which we feel the laboratory should include but are discretionary.

Now, if you're going to actually make something more than reagents, if you're going to make laboratory testing equipment, if you're going to make kits, if you're going to make reagents and kits and equipment that all goes together, then you're going to have to actually show that the test actually has clinical benefit, and the benefit from a diagnostic test is the information it provides, and the risk of the information is that it may not be accurate. You may have false positives, you may have false negatives. If you have to demonstrate that with clinical specimens, then there's a requirement that you follow good clinical practices, which include informed consent, investigational review board oversight, have a protocol, have monitoring of the performance during that time.

Many diagnostic tests do not actually have to submit their protocols to FDA. The ones we're particularly interested in seeing and that we consider not exempt from submitting to us are the ones where there is clinical reliance on the new information of the test. Ovarian cancer, the example I gave earlier, would be such a test.

If you want to go to the market as a completed test, you're going to have to scale up to GMP manufacturing, which means having a quality system, design controls, a CAPA system, which stands for Corrective and Preventive Actions, which means that you have to have a way of monitoring and tracking complaints, resolving complaints, recalling products, changing labeling, issuing alerts and so forth.

As you weigh the relative protections, consumer protections that are required of manufacturers, think back to the somewhat different approach of CLIA to the laboratories, and again when you get back to laboratories developing their own tests, how many of the things that manufacturers develop would be reasonable to expect to have their parallels, and in fact often do have their parallels in the laboratory system?

What do we look at with the premarket applications? Well, products have to be designed properly. You have to specify the design controls that identify how the test will perform, verify that, validate the device performance, and monitor that.

If you come to successful market, it will either be through one of three principal routes. About half of all devices are exempt from premarket review. That doesn't exempt them from all the manufacturing, quality and other types of reporting, but they can go straight to market. I'll talk about Class II and Class III in a moment, but those are the types of applications that FDA reviews, and you cannot go to market until we have done our review.

Then as you go through the life cycle of the product, you have the responsibilities of the product in use of reporting adverse reactions, recalls, labeling revisions, and so forth.

So in summary, if you look at FDA in risk assessment, there are different aspects across the whole life cycle of a product, and because we have products that have to get our approval to come

to market, it's relatively straightforward to identify the investigational phase of a device that requires a 510(k) or a PMA. It's not so clear what the investigational phase is for a laboratory-approved test, and I think that's one of the challenges for us to all think about.

So we look at risk in the investigational phase. We review the performance before it comes onto the market. We review the production and the safety information.

Let me just say a little bit about our arcane review system, courtesy of Congress. This is their town, so we'll say nice things about them. In the beginning there were preamendment devices. In 1976 the law was passed to regulate medical devices, and at that time there may have been as many as half a million medical devices in use. When pharmaceuticals came on the market and required testing in 1962, the default was that the products had to actually demonstrate to review panels of the National Academy of Science that they were probably effective in order to stay on the market. Otherwise they came off, and tens of thousands of products came off.

With devices, the opposite was done. The default was that these products are safe and can in fact be the basis for the approval of future products. In 1979 or 1981, comparing yourself to a 1976 product wasn't so bad. Now, in fact, it works out somewhat differently, although it's still legal to come to the market on the basis that you're as good as something that was on the market in 1976.

The default in the law is if the product is new and novel, that you have to file a premarketing application, which has many parallels in structure to a new drug application, and the standard is that the product must be safe and effective. For a diagnostic device, safe and effective refers to the usefulness of the information.

But one of the things that was done about devices, recognizing that there are between 25,000 and 50,000 new medical devices on the market every year, was that you couldn't require large applications for all of them. So a streamlined application was designed for lower-risk products, and then other products were exempt from any kind of premarket review at all. These are Class I and Class II, the lower-risk class products.

The basis of approval here, they can demonstrate that they're safe and effective, just like a PMA does, but the usual basis for their coming onto the market is to show that they're substantially equivalent to an old product, a product that's already on the market, a product that can go back to products that were on the market as far back as 1976.

This is a little different. It sounds like it's sort of a little bit like a generic drug program where if you're bioequivalent, you can come on the market. But with a generic drug, you want the generic drug and the originator drug to be freely substitutable, because that's how you're going to use them. With devices, it's actually that you have to be at least as good as, and the market pressures in the 510(k) area have worked that most products over time improve and are better than their predicates, but they only have to be as good as something already that was on the market.

Let me talk a little bit about in-house tests. That was all about the device manufacturers per se. In-house tests is a well-established practice with a long history and regulated by CLIA in ways that were described this morning. The analyte-specific reagents that I mentioned earlier when I talked about reagent manufacturers are the building blocks or the active ingredients for many types of in-house tests. The ASR rules and the supervision of manufacturers of reagents was designed to allow for in-house tests with incremental control based on the tests. As I mentioned before, the guidance that was published many years ago was actually a classification guidance saying that most of those products were going to be Class I exempt, there would be no FDA

review prior to coming to market.

What's the regulatory gap with in-house tests? Well, the gap is that the CLIA intent and the FDA were designed to accomplish different goals. The CLIA system is oriented towards the quality of laboratories, and it looks at the whole system of how the laboratories work and the quality of that system, and it focuses on analytic performance and quality control measures. As I have mentioned already, there really is not a definition of investigational, although we heard today proposals to treat genetic tests somewhat differently.

The FDA focuses on devices and the device manufacturers, and it requires evidence of analytical and clinical performance. Sometimes the clinical performance can be implied by linking it to other tests that have already demonstrated clinical performance, and the basic FDA requirement is manufacturing quality standard device by device by device. So between these two standards, there is a bit of a gap. There are things that you have to do for CLIA that device manufacturers don't have to do, and vice versa.

So one of the things that we'll focus on a little bit in the rest of the time is to talk about some of the other FDA consumer tools. I've already talked about almost all of them except for the first one, and that's truth in labeling. This was actually the first FDA approach back in 1906 to providing consumer protections, to simply require that products be accurately described by their manufacturers. The language was that a product's label could not be false or misleading in any particular, and then later they added some additional requirements around fraud.

In summary of my part of the talk before I turn it over to Steve Gutman is just a comment. I noticed this was an historic slide because I've still got HCFA on here. In the HHS, you actually have to pay Tommy Thompson a dollar every time you say HCFA instead of CMS. So I owe the Secretary a buck. Hopefully it won't multiply times all of you.

But if you look at diagnostic tests, one of the real challenges here is you're probably dealing with one of the most regulated areas of medical therapeutics, but it's an overlapping quiltwork as was described in my first slide. It doesn't cover everything, and yet if you'd ask a laboratorian whether or not they're regulated, they have responsibilities to us, to states, to the CLIA program and CMS, to their local IRBs, and not only the devices but the facility itself and each of the professionals in the facility each have a measure of regulation.

So the theme that we would like to develop is how do we get the right balance and how do we get the protections we need without being burdensome and without making a system that already has some redundancies even more difficult in an area where we expect quite a bit of benefit from the medical progress being made in this area?